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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,408	02/21/2002	Lars Abrahmsen	13425-053001	1557

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EXAMINER

PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/081,408	Applicant(s) ABRAHMSSEN ET AL.	
	Examiner Yong D. Pak	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 4, 7 and 9-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 14 and 16 is/are allowed.
- 6) ☒ Claim(s) 1, 4, 7, 9-13, 15 and 17-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 14, 2006 has been entered.

Claims 1, 4, 7 and 9-24 are pending and are under consideration.

Response to Arguments

Applicant's arguments filed August 14, 2006 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 7, 9-10, 15, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al.

Claims 1, 7 and 9-10 are drawn to a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2 or an enzymatically active fragment thereof, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences. Claim 15 is drawn to a vector comprising a polynucleotide encoding said fusion protein and claims 17-19 and 22-24 are drawn to methods of purifying the fusion protein and SSAO.

Smith et al. (form PTO-1449 – reference AYY) teach an amino oxidase that is 100% identical to the semicarbazide-sensitive amino oxidase (SSAO) of SEQ ID NO:2 of the instant invention (Figure 1, page 20 and SwissProt sequence alignment). Smith et al. teach that the transmembrane domain is between residues 5-27 (Figure 1, page 20 and page 21). Art and the specification teach that the soluble from of SSAO lacks

the membrane spanning portion of the wild-type SSAO. Even though Smith et al. teaches the transmembrane domain as including residues 5-27 of SEQ ID NO:27, one of ordinary skill in the art would have also recognized the advantage of using amino acids 29 to 763 of SEQ ID NO:2. The amino acid at position 28 is an Arg. There are numerous proteases in the cell and growth medium that cleaves at arginine residues (Huston et al. – U.S. Patent 5,013,653, Column 10, Table 1). To ensure that the fusion partner and SSAO are not cleaved prematurely, it would have been obvious to fuse the protease cleavage site to a SSAO consisting of amino acids 29-763 of SEQ ID NO:2.

The difference between the reference of Smith et al. and the instant invention is that the reference of Smith et al. does not teach a polynucleotide encoding a secreted fusion protein comprising a signal peptide, a fusion partner, a protease cleavage site and at least one spacer amino acid sequence nor a vector comprising said polynucleotide nor a method of purifying said fusion protein and SSAO.

Huston et al. (U.S. Patent No. 5,013,653 – cited on previous form PTO-892) teach polynucleotide encoding a fusion protein comprising a signal peptide, a target protein and a protease cleavage site between the fusion partner and to the target protein (Column 1). Huston et al. teach that a signal peptide can be used for secretion of the fusion protein and in order protect the target protein from intracellular degradation during expression or isolation/purification(Column 1). Huston et al. also teach that a protease cleavage site can be incorporated between the target protein and any additional fused material (column 1 and 2). Huston et al. also teach a vector comprising

said polynucleotide, a method of producing the target protein and a method of immobilizing the fused target protein (Column 2 and Examples 1-4).

Tudyka et al. (form PTO-1449 – Reference ACCC) teach that GST can be used as a fusion partner that enables dimerization of a target recombinant protein and confer enzymatic reporter activity (abstract and page 2180). Tudyka et al. teach that glutathione S-transferase (GST) from *Schistosoma* that is 100% identical to the GST of SEQ ID NO:4 of the instant invention. Tudyka et al. teach that replacing three of the four exposed cysteine residues in GST (residues 85, 138 and 178) prevents misfolding due to incorrect disulfide bonds (abstract, Figure 2-B, page 2182 and 2185) and the resulting GST mutant is 100% identical to SEQ ID NO:5 of the instant invention. Tudyka et al. also teach that the fusion protein was purified by means of an affinity column with glutathione (abstract) and the GST protein can be proteolytically removed after the fusion protein is produced in the cytoplasm (page 2185).

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising a signal peptide, a fusion partner of Tudyka et al., a soluble form of SSAO of Smith et al., and a protease cleavage site between the fusion partner and to the target protein, as outlined by Huston et al., and also making a polynucleotide encoding a fusion protein comprising a protease, which cleaves at the cleavage site, and a fusion partner. The motivation of making the fusion constructs is to facilitate the secretion, isolation and purification of a soluble SSAO and the protease. The motivation of truncating the transmembrane

domain of SSAO is to produce soluble SSAO, thereby increasing the efficiency of the purification process. The motivation of using amino acids 29-763 of SEQ ID NO:2 is to lower the risk of the target protein from being cleaved prematurely by proteases in the cell or cell culture. The motivation of using the fusion partner of Tudyka et al. is to enable dimerization of SSAO and confer enzymatic reporter activity. The motivation of using the mutant GST of Tudyka et al. is to prevent misfolding of the protein. One of ordinary skill in the art would have had a reasonable expectation of success of making a polynucleotide encoding a fusion protein since the individual proteins incorporated into the fusion proteins are well known in the art and Huston et al. and Tudyka et al. in combination teach detailed steps in making a successful fusion protein and methods of purifying the fusion protein and ultimately the protein of interest.

Therefore, the above references render claims 1, 7, 9-10, 15, 17-19 and 22-24 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that Smith contains no description of a soluble form of SSAO and applicants can not identify a reference to a soluble form of SSAO in Smith. Examiner respectfully disagrees. As indicated in the previous Office Action, while Smith does not teach an isolated soluble form of the enzyme, Smith does identify a transmembrane domain as being between residues 5-27 (Figure 1). With this teaching at hand, one having ordinary skill in the art would have recognized to remove the transmembrane domain to make a soluble form of the protein and one having ordinary

skill in the art would have had a reasonable expectation of success in making such a protein. MPEP 2144.01 states that "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom."

Applicants also argue that the claims are not obvious because the claimed nucleic acid provides a solution to a long-felt but unsatisfied need of a means for purifying to homogeneity and in high amounts a recombinant human soluble SSAO, wherein the claimed nucleic acid permits the recombinant production of milligram quantities of pure, soluble and biologically active human SSAO and Smith describes recombinant expression of full length, membrane-bound SSAO. Examiner notes that the claims do not recite said limitation that the nucleic acid permits for purifying a recombinant human soluble SSAO to homogeneity and in high amounts. Rather, the claims are drawn to a polynucleotide encoding a fusion protein comprising a signal peptide, soluble human SSAO, fusion partner, protease cleavage site and optionally one or more spacer amino acids, with no recitation of the homogeneity or the yield of the encoded SSAO enzyme. Regarding Smith, the rejection is not based on the reference of Smith alone, but the rejection is based on a combination of Smith, Huston et al. and Tudyka et al.

When any claim of an application or a patent under reexamination is rejected or objected to, any evidence submitted to traverse the rejection or objection on a basis not otherwise provided for must be by way of an oath or declaration under this section. No

such oath or declaration has been filed. Nevertheless, Examiner has reviewed the articles mentioned by applicants.

Applicants argue that Holt et al. and Elmore et al. provide evidence of the long-felt but unsatisfied need of a means for purifying high amount of a recombinant soluble SSAO. Examiner respectfully disagrees. First, the claims do not recite a limitation for a "means for purifying high amount of a recombinant soluble SSAO". Second, neither of the references provides evidence of the long-felt but unsatisfied need of a means for purifying high amount of a recombinant soluble SSAO. Holt et al. teaches that SSAO (membrane bound SSAO) "has proved impossible to purify to homogeneity in sufficient yield to permit cofactor identification(abstract). Contrary to applicants arguments, Holt et al. does not provide evidence of a long felt need to purify soluble SSAO, but that sufficient purification of membrane bound SSAO for its cofactor identification is difficult.

Elmore et al. also fails to provide evidence of the long felt need. MPEP 716.04 states that:

"Establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors.

First, the need must have been a persistent one that was recognized by those of ordinary skill in the art.

Second, the long-felt need must not have been satisfied by another before the invention by applicant.

Third, the invention must in fact satisfy the long-felt need."

Applicants have not provided any objective evidence of the long-felt need being a persistent one that was recognized by those of ordinary skill in the art or that it existed

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in the art for a long period of time. Elmore et al.'s purification in high amounts of a soluble SSAO for the first time is not indicative of a long-felt need. "Failure to solve a long-felt need may be due to factors such as lack of interest or lack of appreciation of an invention's potential or marketability rather than want of technical know-how" (MPEP 716.04). Further, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem (MPEP 716.04).

Therefore, as discussed previously, one of ordinary skill in the art would have had a reasonable expectation of success of making a polynucleotide encoding a fusion protein since the individual proteins incorporated into the fusion proteins are well known in the art and Huston et al. and Tudyka et al. in combination teach detailed steps in making a successful fusion protein and methods of purifying the fusion protein and ultimately the protein of interest.

Hence the rejection is maintained.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al. and Zambidis et al.

Claim 11 is drawn to a polynucleotide encoding a fusion protein consisting of a mouse IgG1 heavy chain signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner, a protease cleavage site and one or more spacer amino acid sequences.

Smith et al., Huston et al. and Tudyka et al., in combination teach a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences and a method of purifying the fusion protein, as discussed above.

The difference between the references of Smith et al., Huston et al. and Tudyka et al. is that the combined references do not teach a polynucleotide encoding a fusion protein having a mouse IgG1 heavy chain signal peptide. Huston et al. only teaches using a human IgG1 as a signal peptide in the fusion protein.

Zambidis et al. (cited on previous form PTO-892) teach a mouse IgG1 heavy chain, used as a signal peptide in a fusion protein (abstract).

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising a mouse IgG1 signal peptide. The motivation of making such a fusion construct is to facilitate the expression, secretion and purification of the target protein. One of ordinary skill in the art would have had a reasonable expectation of success since IgG1 or other immunoglobulin proteins are well known and well practiced in the art in facilitating expression and secretion of heterologous proteins.

Therefore, the above references render claim 11 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that since Zambidis et al. does not cure the deficiencies in Smith, Huston, and Tudyka detailed above, the references do not render obvious the nucleic acid of claim 11. Examiner respectfully disagrees. As discussed above, since applicants argument that there is a long-felt need in the art for a means of producing soluble recombinant human SSAO is unfounded, the rejection is maintained.

Claims 12-13 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al. and Brenda Enzyme Database.

Claims 12-13 and 20-21 are drawn to a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner, a protease cleavage site comprising the amino acid sequence of SEQ ID NO:6 and one or more spacer amino acid sequences and a method of purifying the fusion protein.

Smith et al., Huston et al. and Tudyka et al., in combination teach a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences and a method of purifying the fusion protein, as discussed above.

The difference between the references of Smith et al., Huston et al. and Tudyka et al. is that the combined references do not teach a polynucleotide encoding a fusion protein having a protease cleavage site comprising the amino acid sequence of SEQ ID NO:6.

Huston et al. teaches that many different protease cleavage sites can be introduced into the fusion protein (Columns 9-11). Brenda Enzyme Database (EC 3.4.22.28 – form PTO-892) teach a 3C protease from Coxsackievirus that is 100% identical to SEQ ID NO:6 of the instant invention. The Database also teaches a picornavirus 3C protease and a rhinovirus 3C protease (pages 3-4). There are many types of protease cleavage sites and 3C proteases is one of the many enzymes capable of safely cleaving a fusion partner from the target protein.

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising any of the 3C proteases listed in the Brenda Enzyme Database. The motivation of incorporating a cleavage site between the SSAO and GST is to cleave off the GST protein after the fusion protein is produced in the cytoplasm. One of ordinary skill in the art would have had a reasonable expectation of success since 3C proteases are well known and have been widely used in cleavage sites between target proteins and additional fused material.

Therefore, the above references render claims 12-13 and 20-21 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that since Brenda does not cure the deficiencies in Smith, Huston, and Tudyka detailed above, the references do not render obvious the nucleic acid of claim 1. Examiner respectfully disagrees. As discussed above, since applicants argument that there is a long-felt need in the art for a means of producing soluble recombinant human SSAO is unfounded, the rejection is maintained.

Allowable Subject Matter

Claims 14 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

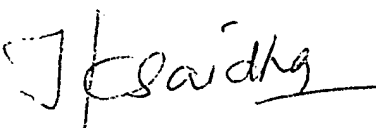
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Yong D. Pak
Patent Examiner 1652


Tekchand Saidha
Primary Patent Examiner 1652